Fibrosing colonopathy in an adult owing to over use of pancreatic enzyme supplements

D S Bansi, A Price, C Russell, M Sarner

Abstract
A woman, then in her late 20s, underwent a cholecystectomy in 1962 for gallstone disease and subsequent common bile duct stones were managed endoscopically. However, because of unrelenting pain, a pylorus preserving pancreaticoduodenectomy was done in 1990 and in the following years the patient took large amounts of pancreatic enzyme supplements. She developed large bowel obstruction in 1997 and a right hemicolectomy was undertaken. Histology confirmed fibrosing colopathoy of the ascending colon and caecum. Her pancreatic enzyme dose was reduced and her subsequent course has been uncomplicated.

Case report
The woman developed recurring right upper abdominal pain in her late 20s while working as a teaching nun. In 1962 she presented with episodes of jaundice, and a cholecystectomy with common bile duct exploration was performed. In 1972, jaundice recurred for which she had a transduodenal sphincteroplasty for papillary stenosis. From 1983 to 1987 she had recurrent episodes of pain and represented with jaundice in 1987. On this occasion, an endoscopic sphincterotomy was complicated by acute pancreatitis. Thereafter she was never free of pain and was commenced on Creon (Solvay Healthcare Ltd) in 1988. In 1990 her medication was changed to Pancrease (Janssen-Cilag Ltd) of which she took 30 capsules (equivalent to 3000 BP units lipase activity/kg) per day. However, because of unrelenting pain she underwent a pylorus preserving pancreaticoduodenectomy in 1990. The resected pancreatic tissue showed intralobular, perilobular, and periductal fibrosis accompanied by focal atrophy of the gland. For most of that year she had three to four loose motions per day for which she took up to 12 Pancrease capsules (equivalent to 1100 BP units lipase activity/kg) per day. A low fat diet was recommended. By December 1990 her diarrhoea had worsened and the Pancrease was increased to 60 capsules (equivalent to 5300 BP units lipase activity/kg) daily. Medication was changed to Nutrizym GR (Merck Bio), of which she was taking up to 100 capsules (equivalent to 17 700 BP units lipase activity/kg) per day by June 1991. In March 1992, her treatment was changed to Nutrizym 22; she was prescribed 50 capsules (equivalent to 38 000 BP units lipase activity/kg) per day. Her condition stabilised with three to five bowel actions per day until mid-1995 when severe abdominal pain developed with a possible mass in the right iliac fossa. At laparotomy on 3 November 1995, a diagnosis of Crohn’s disease of the ascending colon was made on full thickness biopsy. Subsequent investigations, including a barium enema and barium follow through meal, were normal.

Mesalazine 400 mg three times daily was commenced, together with a low fat, low residue diet, and a reduction of the Nutrizym advised. However, her symptoms persisted. A computed tomography scan in February 1997 showed a thickened and dilated loop of large bowel. At laparotomy on 25 April 1997, the right colon was a solid mass embedded in fibrous tissue. A right hemicolecotomy was performed. Histology showed submucosal fibrosis, loss of definition of the muscularis mucosa with partial replacement by fibrous tissue, and intermittent fibrosis of the inner third of the circular muscle. Fibrosis on the serosal aspect of the caecum and ascending colon was noted. The changes were associated with a mild chronic inflammatory cell infiltrate including numerous eosinophils; there was loss of definition of the muscularis mucosa extending throughout the colon to the distal resection margin and involving the terminal ileum. The histological features were consistent with the diagnosis of fibrosing colonopathy (fig 1).

Subsequently her bowel habit has improved, on a normal diet, with no diarrhoea on a

Abbreviations used in this paper: NSAID, non-steroidal anti-inflammatory drug.
maximum daily dose of 25 capsules of Creon, equivalent to 3000 PhEur units lipase activity/kg. At colonoscopy in early 1999, the remaining colon and 30 cm of neoterminal ileum were completely normal. On account of the possible association of pancreatitis with cystic fibrosis, a cystic fibrosis gene carrier screen was performed. She was negative for each of the following mutations which, between them, should detect 90% or more of white carriers: 1717-G→A, G542X, W1282X, N1303K, ΔF508, 3849+10kbC→T, 621+1G→T, R553X, G551D, R117H, R1162X, and R334W.

Discussion
Atrophy or resection of a substantial part of the pancreas, with consequent lipase deficiency, produces fat maldigestion and hence malabsorption which can only be remedied by exogenous lipase. Early replacement therapy contained inadequate quantities of lipase. In 1991, new formulations of lipase became available with increased quantities of active lipase (up to 25 000 PhEur units) per capsule, with improved ease of administration. In 1994, five cases of submucosal fibrosis affecting the proximal colon of children with cystic fibrosis were described, with further subsequent reports attributing the colonopathy to the higher dose of lipase. The term “fibrosing colonopathy” was introduced to describe this complication of cystic fibrosis involving a stricture or prestriction state with varying degrees of stenosis in the colon. Previously, the entity has been reported only in children; this report describes an adult with an identical histological appearance.

The pathogenesis of this process remains uncertain. Histological features do not resemble the strictures described with potassium chloride preparations or non-steroidal anti-inflammatory drugs (NSAIDs) which are characterised by ulceration and short segment fibrosis. Detailed review of the patient’s medication did not reveal any drugs or other predisposing factors to account for the colonopathy. Moreover, the colonopathy is independent of cystic fibrosis (the patient had no cystic fibrosis gene mutations), but does appear to be dose dependent. Variations in blood supply, nutrients (especially short chain fatty acids), and damaging metabolites partly dependent on diet may also explain individual variations in susceptibility to high dose enzyme intake. More recently, it has been suggested that the methacrylic acid copolymer Eudragit L30 D55 could be the key factor in pathogenesis, following the description of fibrosing colonopathy in two children who had been treated with high doses of the low strength enzyme preparation Nutrizym GR. This enteric coating material is also used in preparation of the high strength enzyme preparations Pancrease HL, Nutrizym 22, and Panzytrat 25000, previously found to be associated with the condition, but not in products such as Pancrease, Pancrex V, Creon, and Creon 25000 which have not been associated with the condition. It is interesting to note that our patient had been treated with a variety of different formulations, including Nutrizym GR and Nutrizym 22, both of which have this enteric coating.

In conclusion, this woman had high dose enzyme replacement for five years. Although we do not yet know if there is a safe upper limit of dosage for adults, this report suggests that it would be wise to keep within the recommended guidelines for children and not exceed 10 000 units of lipase per kg per day if the

Figure 1 (A) Fibrosis of the submucosa with replacement of the muscularis mucosae. The overlying mucosa is inflamed, the infiltrate containing many eosinophils. Muscle bundles of the muscularis propria, caught up by the fibrosis, are just visible at the base. (B) Uninvolved full thickness normal colon at the same magnification.
Pancreatic enzyme supplement induced fibrosing colonopathy

unfortunate side effect of fibrosing colonopathy is to be avoided.

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